REMARKS

Claims 90-178 are pending in the instant application.

STATEMENT OF THE SUBSTANCE OF THE INTERVIEW

Applicant and Applicant's representatives thank Supervisory Patent Examiner Gary Benzion and Examiner Suryaprabha Chunduru for the courtesy of the telephonic interview of January 25, 2007 (the "Interview") in connection with the above-identified application. Pursuant to 37 C.F.R. § 1.133 and M.P.E.P. 713.04, Applicant presents this interview Summary Record of the Interview between Supervisory Patent Examiner Gary Benzion and Examiner Suryaprabha Chunduru, and Applicant's representatives Adriane M. Antler, Muna Abu-Shaar and David Gay, in connection with the above-referenced application.

During the Interview, the Office Action dated August 7, 2006 ("Office Action") was discussed. Dr. Antler explained the features common to all the independent claims directed to populations of thirty or more unique labels, substantially as set forth hereinbelow. Dr. Antler also explained why the prior art relied upon by the Examiner in the Office Action, U.S. Patent No. 5,679,519 by Oprandy ("Oprandy) and European Patent Application Publication 0 292 128 A1 by Segev ("Segev"), alone or in combination, did not teach or suggest the subject matter of the instant claims. Supervisory Patent Examiner Gary Benzion acknowledged Applicant's arguments, and stated that he wished to consult with Exminer Chunduru and other primary examiners to determine whether they wished to suggest any changes to the claim language. Subsequently, Attorneys for Applicant received a voicemail message on January 30, 2007 from Examiner Chunduru, following her discussions with another primary examiner and Supervisory Patent Examiner Gary Benzion, suggesting that the response to the Office Action be filed, as discussed with the Examiners in the Interview, without any claim amendments.

Details of the arguments presented in support of patentability are found hereinbelow.

THE REJECTION UNDER 35 U.S.C. § 103 should BE WITHDRAWN

The Present Claims

Pending claims 90-156 and new claim 178 are directed to diverse populations of labels. The diverse populations of the invention have several "basic" features in common:

(1) the *populations comprise at least 30* (or, in claim 152, at least 100) *unique labels*, which as defined in the specification (see ¶ [0021] of US20030013091 A1) means that each unique label "has a detectable signal that distinguishes it from other labels in the same mixture." Thus, there are 30 or more labels in the population, each of the 30 or more labels giving rise to a signal that is distinguishable from the other 29 or more labels.

(2) wherein each of said *unique labels comprises a molecule, said molecule comprising a plurality of genedigits* (defined as "region of pre-determined nucleotide or amino acid sequence that serves as an attachment point for a label," see ¶ [0017] of US20030013091 A1), each genedigit being of predetermined sequence. It should be noted that the claims require that the at least two genedigits are in a single molecule.

(3) wherein *at least two* (or, in claim 152, at least four) of said *genedigits are each attached to a respective anti-genedigit* (defined as "a nucleotide or amino acid sequence or structure that binds specifically to the gene digit," see ¶ [0017] of US20030013091 A1), each said anti-genedigit being *attached to at least one label monomer*.

Thus, claims 90-156 and 178 provide for diverse populations of (*e.g.*, 30 or more) labels distinguishable by virtue of the attachment of label monomers to genedigits via the specific binding of anti-genedigits to which the label monomers are attached. The modular permutations of genedigit/anti-genedigit combinations gives rise to diverse populations of unique, *i.e.*, distinguishable, labels, starting even from a small number of label monomers. The diverse populations of labels can be attached to target-specific sequences to detect analytes of interest. See, *e.g.*, US20030013091 A1 at ¶¶ [0028], [0029] and [0079] and Figure 1. Accordingly, each of the *30 or more* labels in the population are *distinguishable in signal* from the other 29 or

more, each label has at least 2 genedigits that are in a *single molecule*, each of the at least 2 genedigits being attached to a label monomer via the anti-genedigits (which are attached to the label monomer).

Claims 157-177 are directed to labeling kits useful for generating the diverse populations of the invention.

The Present Rejection

Claims 90-178 are rejected under 35 U.S.C. § 103 as obvious over U.S. Patent No. 5,679,519 by Oprandy ("Oprandy) and European Patent Application Publication 0 292 128 A1 by Segev ("Segev").

According to the Examiner, Oprandy teaches:

> ...a multi-labeled probe complex comprising a platform molecule carrying a plurality of labels comprising plurality of genedigits, each genedigit being a predetermined sequence (oligonucleotides) wherein gene digit is attached to an anti-gene digit (complementary sequences or oligonucleotide probe sequences).

Office Action at page 2, citing column 4, lines 28-34 and column 6, lines 20-47 of Oprandy. The Examiner also contends that Oprandy also teaches other aspects of the invention (Office Action at pages 2-4), but does not teach a diverse population of thirty or more labels.

The Examiner then goes on to say that "Segev teaches labeled DNA molecules with multiple fluorescent signals (reporter groups) wherein Segev discloses that unique labels or dyes comprise an array bearing 2^{n-1} reporter groups having unique emission spectra (see page 5, lines 36-49)" (Office Action at page 4).

The Examiner concludes that one of skill in the art would have been motivated

> "to combine the diverse population of molecules comprising genedigits and anti genedigits as taught by Oprandy. with an inclusion of array labels as taught by Segev to develop a sensitive and improved population of molecules with distinct labels. An ordinary artisan would have had a reasonable expectation of success that such modification of the method taught by Oprandy in a manner as taught by Segev because Segev explicitly taught that use of a mixture of unique labeled probes or dyes comprise unique emission spectra (see page 6, lines 2-4) which is unique to the specific set or population (see page 23, lines 17-25); unique labels comprise mixture of two or more (64-40,960) different or distinctly labeled particles created through variation of the amount of or type of dye (see page 17,

lines 28-37, page 18, lines 1-15, page 6, lines 23-33) and such modification of the method is considered obvious over the cited prior art in the absence of secondary considerations."

Office Action at page 5.

The Examiner contends that the present claims are obvious over Oprandy in view of Segev. Applicant submits that the Examiner's assessment of Oprandy and Segev is in error, and the pending claims are not obvious over the references, as discussed below.

The Law Of Obviousness

To establish a *prima facie* case of obviousness, the teachings of the prior art must provide one of ordinary skill in the art with some suggestion or motivation to make the claimed composition. *In re Rijckaert*, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). For a claimed invention to be deemed obvious in view of a prior art disclosure, the prior art disclosure must, firstly, give rise to a *suggestion of or motivation for* the claimed subject matter. Assuming such a suggestion or motivation is found, and the invention is thus arguably "obvious to try" to achieve, only then does one reach the question of whether one of ordinary skill in the art would have had a reasonable expectation of success in achieving it. *See e.g., In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Both the suggestion of the claimed invention and the expectation of success must be in the prior art, not in the disclosure of the claimed invention. *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988).

"Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999), abrogated on other grounds, citing to *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). In particular, the Examiner cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). Care must be taken to avoid hindsight reconstruction by using Applicant's disclosure "as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result" of the claims in question. *Grain*

Processing Corporation v. American Maize-Products Company, 840 F.2d 902, 907 (Fed. Cir. 1988), citing *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1012 (Fed. Cir. 1983).

Applicant submits that the Examiner, in raising the obviousness rejections, is employing a hindsight reconstruction without casting her mind to the state of the art at the time of filing the present application. As stated above, such hindsight reconstruction cannot be used for determining obviousness. Neither of the references cited by the Examiner, alone or in combination, suggests or provides motivation for the presently claimed invention, let alone with a reasonable expectation of success. In particular, neither Oprandy nor Segev suggests more than one unique label containing the basic features described above, *i.e.*, distinguishable in signal from other labels in the population and containing at least two genedigits that are part of the same molecule, each attached to an anti-genedigit to which is attached a label monomer. Each of these references is discussed in turn below to demonstrate that, whether alone or in combination, these references do not provide any suggestion of, or motivation for, the claimed invention.

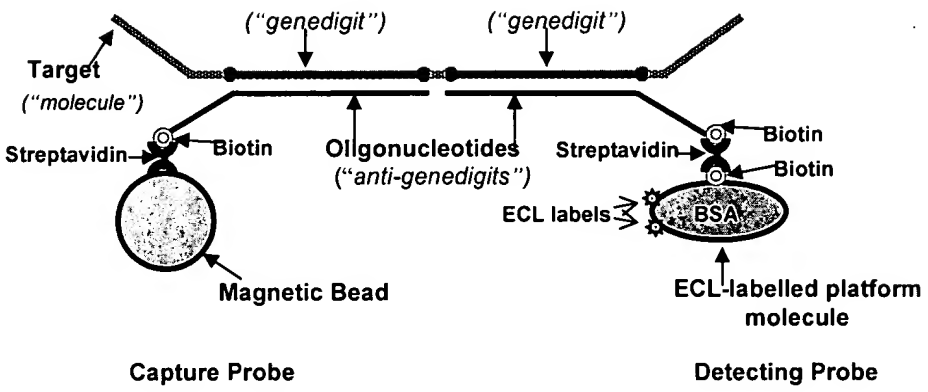
Oprandy and Segev Do Not Suggest or Provide Motivation for the Present Invention

Oprandy

Oprandy generally relates to detection of target nucleic acids using a nucleotide probe complex, containing a platform molecule carrying multiple electrochemiluminescent ("ECL") labels and oligonucleotide probes, that enhances the ability to detect low level samples in ECL assays (Oprandy at Abstract and at Summary of Invention, column 4, lines 28-63). In a preferred embodiment, the platform molecule is bovine serum albumin (BSA) complexed to biotin molecules for attachment to the oligonucleotide probe via avidin-biotin connections (Oprandy at column 5, lines 42-47). Accordingly, "detecting" oligonucleotide probes with target-specific sequences are bound to the platform molecule, for example by use of biotin-labeled oligonucleotides that are attached to a biotinylated BSA platform that has been capped with streptavidin (column 5, lines 50-51 and column 6, lines 26-33). Additionally, ECL labels are attached to the platform molecule by chemical means (column 6, line 58 through column 7, line 3). Magnetic beads carrying capture oligonucleotide, preferably with sequences complementary to different portions of the target than the detecting probes, are also used (column 7, lines 28-30). The magnetic beads may be streptavidin-coated and the capture oligonucleotide biotinylated to

allow attachment of the magnetic beads to the capture oligonucleotides (column 8, lines 16-19). According to the teachings of Oprandy, target nucleic acids are detected in one- or two-step processes (column 7, line 55). In the one-step process (Format 1), the streptavidin-capped platform molecule to which oligonucleotides have been attached and which has been labeled with ECL labels is incubated in the ECL apparatus with the capture probe-bound magnetic beads and the target sample (column 7, lines 55-61). Binding to the target by the probes is indicated by the presence of localized label at the probe in the ECL apparatus (column 7, lines 61-64). In the two-step process (Format 2), the capture probe and the detecting probe are introduced into the ECL system sequentially instead of simultaneously (column 8, lines 12-32). Oprandy also teaches alternative embodiments to Formats 1 and 2; however, the various embodiments (Format 1 variant, Format 3 and Format 4) taught by Oprandy relate to different methods of forming the hybridization complex, such as by a different order of addition of components of the capture probe and the detecting probe. Ultimately, though, all formats taught by Oprandy result in the same basic hybridization complex: a target molecule bound to both a capture oligonucleotide (attached to a magnetic bead) and a detection oligonucleotide (attached to an ECL label-bound platform molecule).

Regardless of which disclosed format of the Oprandy assay is employed, the result of the hybridization is a hybridization complex containing a target molecule, a magnetic-bead bound capture oligonucleotide, and an-ECL labeled platform-bound detection oligonucleotide. This resulting complex is illustrated in Figures 4-8 of Oprandy, and is schematically represented in the following figure:



Attempted "best fit" of the hybridization complex of Oprandy to core features of claims

As illustrated in the figure above, even when analogizing the components of Oprandy's hybridization complex in an attempt to "best fit" it to elements of the present claims, the hybridization complex of Oprandy is --at best-- *no more than a single unique label* (as that term is construed in the present claims): this hybridization complex produces a single detectable signal, which is generated by the activation of the ECL labels in the ECL device (as explained in the Background section, for example at column 2, line 22 through column 4, line 24).

Applicant points out that in contrast to the diversity of labels produced by the present invention, Oprandy at best teaches making and using only a single unique hybridization complex that contains the basic elements of a label of the invention and has a signal distinguishable from any other labels in the population. This is because the goal of Oprandy is to increase signal intensity emanating from a single target molecule, rather than detecting a plurality of different target molecules that can be distinguished from one another.

Oprandy's goal of increasing signal intensity and assay sensitivity is clear. For example, in the Summary of the Invention at column 4, lines 35-39, 52-54 and 56-58, Oprandy states that:

> The concept of increasing the number of signal producing molecules associated with a probe to increase signal has previously been disclosed, notably for situations where the probes are based on the use of antibodies. This approach has limited utility, however...
>
> Central to its many advantages, the invention provides a substantially increased signal with a concomitant reduction in background....This process dramatically increases signal-to-noise in assays and thereby profoundly enhances the sensitivity of these assays.

In addition, in the Background of the Invention at column 4, lines 16-24, Oprandy teaches that:

> While the ECL process, using amplification is effective, there is a need to be able to effectively carry out the ECL assay without amplification for reasons noted earlier. The sensitivity of non-amplified nucleic acid assays to date has been between 10^3 -10^6 copies of DNA (data not shown). Accordingly, the principal object of the present invention is to provide such an ECL assay.

Thus, Oprandy's objective is to provide a sensitive ECL assay without the need for nucleic acid amplification. In other words, the purpose of Oprandy's assay is to provide a single amplified signal from a target molecule, rather than to generate a diversity of distinguishable signals for a diversity of target molecules.

With respect to the types of "label monomers" to which the platform molecule can be attached, Oprandy teaches various ECL labels that may be used (column 6, lines 34-47), but it is clear from the teachings of Oprandy that only one of such labels is used per assay mixture, in multiple copies, in order to fulfill the goal of signal amplification. Oprandy exemplifies his invention by use of the single label: ruthenium II tris bipyridil ($Ru(bpy)_3^{2+}$), which when oxidized in the presence of TPA emits a detectable signal (see Oprandy at column 4, line 65 through column 5, line 7). Oprandy provides no suggestion to create a population of different distinguishable signals from different ECL labels.

Thus, at best, the various embodiments taught by Oprandy result in the formation of at most *one* probe-target hybridization complex having the structural basic characteristics of a label of the invention that produces a single distinguishable signal. Thus, *at best*, Oprandy discloses a single unique label of the invention, and does not teach or suggest creating a population of more than one such "unique label."

Nowhere in the disclosure of Oprandy is there a teaching or suggestion of the idea of generating a diversity of labels in the same population with both the distinguishable signals *and* basic structural features specified in the instant claims. Oprandy does not teach or suggest creating distinguishable signals generated by a defined structure to detect different target molecules. Oprandy's probes contain multiple ECL labels attached to a single platform molecule which results in an increase in signal and reduction in background (see Summary of the Invention at column 4, lines 28-64) that enable the user to detect a nucleic acid present in a small

amount without the need for nucleic acid amplification (see, for example Oprandy at column 4, lines 10-25). However, Oprandy does not provide any motivation for producing a population comprising a plurality of distinguishable labels as claimed herein.

Therefore, there is no teaching or suggestion in Oprandy of a population of thirty or more (as claimed in claims 90-94 and 151) or one hundred or more (as claimed in claim 152) unique labels, each comprising a molecule with a plurality of genedigits, in which at least two genedigits (or, in the case of claim 152, at least four genedigits) are each attached to a respective anti-genedigit, each anti-genedigit being attached to at least one label monomer, as specified by the claims. Nor does Oprandy even suggest how such a diverse populations of 30 or more unique labels, *i.e.*, each distinguishable from the other 29 or more, can be achieved.

Thus, Oprandy does not teach or suggest the subject matter of any of independent claims 90-94, 151 and 152.

With respect to claim 157, Oprandy does not teach or suggest a labeling kit comprising in one container thirty or more unique molecules with a plurality of genedigits of predetermined sequence and in one or more other containers a plurality of respective anti-genedigits, each attached to at least one label monomer, for the same reasons as discussed above. Thus, Oprandy also does not teach or suggest the subject matter of independent claim 157.

For the foregoing reasons, the dependent claims are also nonobvious over Oprandy.

Segev

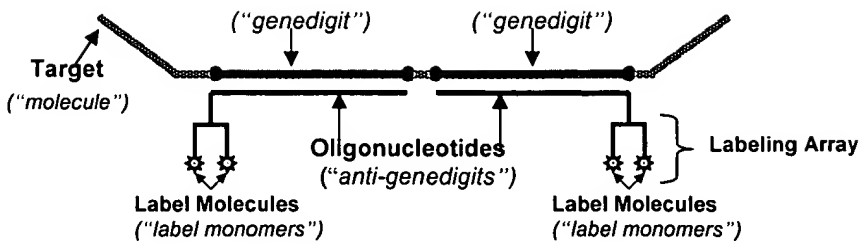
Segev does not remedy the deficiencies of Oprandy. Segev is directed to methods of generating nucleic acid probes with multiple terminal reporter groups attached via branched networks (Segev at Abstract) referred to as labeling arrays (see, *e.g.*, page 5, lines 26-35).

Segev's probes are illustrated in Figure 1 of Segev. As shown in Figure 1 and explained at page 4, lines 8-20, each probe contains a target-specific sequence and a labeling array, the labeling array containing one or more phosphate groups (P) and one or more reporter molecules (R) attached via linker molecules and polyhydroxyl branching molecules. Thus, the reporter groups are attached to the target-specific sequences through chemical reactions, and not through genedigit/anti-genedigit configurations. Nowhere in Segev is there is description or a suggestion of a modular, sequence-specific genedigit/anti-genedigit attachment of label monomers to a

molecule. Moreover, like Oprandy, Segev's disclosed methods and compositions are to achieve signal amplification of a single signal by use of multiple copies of a single reporter molecule (label monomer). Indeed, in the text cited by the Examiner, when Segev states that "[i]n principle, there is no limit to the number of reporter groups that can be attached to the molecular probes of the invention" (Segev at page 5, lines 36-37), Segev is referring to the number of copies of a reporter molecule attached to a given probe to increase the signal strength of that probe (see page 5, lines 41-45).

Critically, although Segev describes different types of reporter molecules that may be used, *e.g.*, radioisotopes, chemiluminescent molecules, bioluminescent molecules, fluorescent molecules, and biotin (Segev at page 4, lines 28-52), there is no suggestion in Segev to use a plurality of distinguishable signals in a single assay mixture so as to create a population of distinguishable labels. As discussed above, Oprandy suffers from this very same defect.

The Examiner cites to page 5, lines 36-49 of Segev as providing for the use of "a mixture of unique labeled probes" (Office Action at page 4). Applicant submits that although Segev teaches the use of multiple probes in the section referred to by the Examiner (at page 5, lines 44-49), the probes do not form unique labels, as that term is used in the claims, because hybridization complexes formed by the different probes do not give rise to distinguishable signals. In particular, Segev suggests in the section cited by the Examiner attaching a smaller number of reporter molecules to different oligonucleotides with different target-specific sequences corresponding to different portions of the same target molecule, for the purpose of increasing signal strength from the target molecule (see page 5, lines 44-49). Analogizing Segev's hybridization complex in which a target molecule is hybridized to multiple probes, each with multiple reporter molecules, in an attempt to "best fit" it to elements of the present claims, the hybridization complex of Segev, like that of Oprandy, is *no more than a single unique label* (as that term is construed in the present claims):



Attempted "best fit" of Segev multiple probe embodiment to core features of claims

This multiple probe embodiment of Segev is exemplified in Example 3 of the specification beginning at page 10. In Example 3, ten different probes to the HSV-1 thymidine kinase gene were synthesized, each containing 4 biotin molecules. The probes were used singly or in combination (probes 1-5 and probes 1-10) in hybridization reactions with HSV-1 DNA. HRP-labeled avidin and a colorimetric substrate assay were used to generate a single signal. Thus, all the probes employed in the multiple probe embodiments (using a combination of probes 1-5 or probes 1-10) were labeled with the same label monomer (biotin), and HSV-1 DNA was detected using an aggregate signal from all the probes. Segev concludes that "the strength of the [colorimetric] signal observed was greatly increased when mixtures of probes complementary to different regions along the target DNA were used" (Segev at page 11, lines 42-44).

Thus, Segev's multiple probe embodiment amplifies the signal from a target molecule by aggregating the signal from multiple copies of a single type of label monomer, and does not make or use a mixture of "unique" labels, as that term is defined in the present application (see ¶ [0021] of the published specification) to mean having a detectable signal distinguishable from other labels in the same mixture.

In conclusion, neither Oprandy nor Segev teaches more than one unique label of the invention, let alone more than 30 unique labels. Both Oprandy and Segev seek to amplify a single signal, whether by binding multiple ECL labels to a platform molecule (as in Oprandy) or by generating a branched terminal structure containing multiple reporter groups (as in Segev). Thus, Oprandy and Segev, whether singly or in combination, do *not* suggest the presently claimed invention. There is no suggestion in either Oprandy or Segev of the use of individual

molecules, each containing at least two genedigits, attached to respective anti-genedigits attached to label monomers, to create at least 30 labels, each with a distinguishable signal, in a population.

In view of the foregoing, Applicant submits that the rejection under 35 U.S.C. § 103 is in error and should be withdrawn.

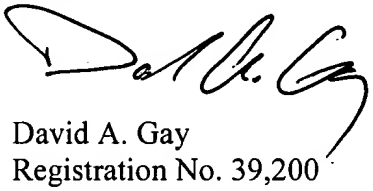
CONCLUSION

Applicant respectfully requests that the Examiner reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney if a telephone call would help resolve any remaining items.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

McDERMOTT WILL & EMERY LLP



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